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10/534,915	05/10/2005	Gerd Haberhausen	21719-US	9560

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EXAMINER	
MUMMERT, STEPHANIE KANE	
ART UNIT	**PAPER NUMBER**
1637	
NOTIFICATION DATE	**DELIVERY MODE**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)
	10/534,915	HABERHAUSEN ET AL.
	Examiner	**Art Unit**
	STEPHANIE K. MUMMERT	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *20 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 20, 2010 has been entered.

Applicant's amendment filed on April 20, 2010 is acknowledged and has been entered. Claims 1-3 and 5-7 are pending.

Claims 1-3 and 5-7 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made NON-FINAL.

Previous Grounds of Rejection - adjusted to address arguments

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/532319 (‘319 application). While these claims are not identical, they are not patentably distinct from one another. The claims of the copending ‘319 application are directed to a method for detecting the presence of bacterial pathogens in clinical samples, comprising steps directed to the isolation of nucleic acids, amplification and quantifying the amount of nucleic acids comprising a sequence that is specific for a bacterial pathogen, wherein the method of quantification comprises amplification, monitoring of amplification through a hybridization probe and through monitoring temperature dependence of hybridization. The claims of the ‘319 application also is directed to “multiple” hybridization probes including SEQ ID NO:3-5 and 8-9. The claims of the instant application are directed to a similar method directed to the amplification and detection of bacterial pathogens. The differences between the current application and the ‘319 application lie in the specific recitation of analysis of specific aliquots of clinical specimens and comprising the use of multiple hybridization reagents in the instant application as contrasted with the real-time monitoring of amplification in the copending application, which falls within the scope of the amplification, detection and monitoring of temperature dependence of hybridization in the instant application. While the copending '319 application does not recite 16S/23S or 18S/26S rRNA spacer sequence, this preselected sequence of the instant application falls within the scope of the claim as recited in the copending application. Furthermore, while the copending application does not specify the specific rRNA spacer sequence as comprising either 16S/23S or 18S/26S rRNA sequences, Jannes teaches specific detection of 16S/23S rRNA sequences.

Considering the teaching by Jannes, "the spacer region situated between the 16S rRNA and the 23S rRNA gene, also referred to as the internal transcribed spacer (ITS), is an advantageous target region for probe development for detection of pathogens of bacterial origin" (p. 1-2), therefore it would have been prima facie obvious that 16S/23S or 18S/26S rRNA sequences fall within the scope of the rRNA sequences claimed in the copending application.

This is a provisional obviousness-type double patenting rejection.

Claim Interpretation

The specification does not define the term "internal control" or "internal control template." Instead, the specification merely states, "it has been proven to be particular advantageous, if an internal control template is added. Usually, said control template comprises a selected sequence with primer binding sites complementary to at least one set of amplification primers used for amplification of the target nucleic sequences" (p. 20, line 30 to p. 21, line 4). Therefore, while Applicant argues that the internal control template comprises shared primer binding sites, neither the claims nor the specification require this limitation of the claims, only that this is usually the case. In the absence of such limitations, the term will be given a broadest reasonable interpretation, as reading on both control templates that are co-amplified using different primers for amplification of the target and control templates, and on control templates that are co-amplified using shared primer sites in the target and control templates.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-3 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards et al. (J. Clin. Micro., 2001, vol. 39, no. 9, p. 3047-3051, IDS reference) in view of Forsman et al. (Microbiology, 1997, vol. 143, p. 3491-3500), Bergeron et al. (NEJM, 2000, vol. 343, no. 3, p. 175-179), Bergeron et al. (US Patent 6,001,564; December 1999, "Bergeron '564" herein), Kunsch et al. (WO98/50555; November 1998, "Kunsch '98" herein), Kunsch et al. (EP786519; July 1997, "Kunsch '97" herein), Naimi et al. (Sys. Appl. Micro. 1999, 22(1):9-21), Lowe et al. (Nucleic Acids Research, 1990, vol. 18, no. 7, p. 1757-1761) and Buck et al. (Biotechniques (1999) 27(3):528-536). Edwards teaches detection of Staphylococci using plural hybridization probes through monitoring of hybridization (Abstract).

With regard to claim 1, Edwards teaches a method for identification of a pathogenic organism from a predetermined group of pathogens, comprising:

a) at least partially purifying nucleic acid from a clinical sample (p. 3048, col. 1, where DNA was extracted from type strains and clinical isolates),

b) subjecting at least a first aliquot of said clinical specimen to at least a first amplification and detection reaction in one reaction vessel (p. 3048, 'Light Cycler assays' heading, where the amplification and detection are carried out in the same vessel) comprising:

ba) at least a first set of amplification primers capable of amplifying a pre-selected nucleic acid sequence comprising the 16S rRNA region from several or all members of said predetermined group of pathogens (p. 3048. Table 2, where primers for amplification of the samples are provided), wherein said predetermined group of pathogens comprises members of two or more genera (p. 3048, Table 1, where a variety of pathogens from two or more genera are detected),

bc) a plurality of hybridization reagents, said reagents together being capable of specifically detecting a pre-selected nucleic acid sequence comprising the 16S rRNA region from all members of said predetermined group of pathogens (p. 3048, Table 2, where the probes are designed to detect the pathogens including staphylococcus and micrococcus), said detection step comprising:

bca) monitoring hybridization of each of said hybridization reagents at a pre-selected temperature, said hybridization being indicative for at least the genus of said pathogen present in the sample (Figure 1, where the hybridization of the probes at preselected temperatures is observed and monitored for each of the probes; p. 3048, col. 1, ‘LightCycler assays’ heading, where it is noted that "fluorescence readings were taken after annealing at 55oC for 1 s" which was followed by melt curve analysis and where it is noted that the hold at the first temperature before the melt meets the limitation of the claim);

bcb) monitoring temperature dependence of hybridization, said temperature dependence being indicative of at least the species of said pathogenic organism (Figure 1, where the hybridization of the probes at preselected temperatures is observed and monitored for each of the probes; p. 3049, col. 1, where the indication of species for each melting temperature is provided; see Table 3 and 4);

and wherein said amplification and detection reaction is indicative of the identity of said pathogenic organism from a predetermined group of pathogens (Figure 1, where the hybridization of the probes at preselected temperatures is observed and monitored for each of the probes; p. 3049, col. 1, where the indication of species for each melting temperature is provided; see Table 3 and 4).

With regard to claim 2, Edwards teaches an embodiment of claim 1, further comprising subjecting at least a second aliquot of said clinical specimen to at least a second amplification and detection reaction in a different reaction vessel from said first aliquot of said clinical specimen being subjected to said first amplification and detection reaction in two different reaction vessels (p. 3048, col. 1, where multiple clinical samples were analyzed and where each individual specimen would be analyzed by amplification and detection in a separate aliquot and a separate reaction vessel).

With regard to claim 3, Edwards teaches an embodiment of claim 2, further comprising subjecting at least a third aliquot of said clinical specimen to at least a third amplification and detection reaction in a different reaction vessel from said first aliquot of said clinical specimen being subjected to said first amplification and detection reaction, and said second aliquot of said clinical specimen being subjected to said second amplification and detection reaction (p. 3048, where multiple clinical samples were analyzed and where each individual specimen would be analyzed by amplification and detection in a separate aliquot and a separate reaction vessel).

With regard to claim 7, Edwards teaches an embodiment of claim 2, wherein said first amplification and detection reaction and said second amplification and detection reaction are performed with the same thermocycling profile (p. 3048, col. 1, where the amplification reaction

conditions applied to each of the clinical samples are the same, even if they are amplified and detected in the same or separate reaction vessels).

Regarding claim 1, Edwards does not teach that the primers target the spacer region between 16S and 23S rRNA. Edwards also does not teach the specific plurality of hybridization probes of SEQ ID NO:3-5 and 8-9 targeted to the detection of enterococcus and staphylococcus species. Forsman teaches sequencing and amplifying the 16S-23S rRNA spacer region for specific detection of Streptococcus and Staphylococcus species (Abstract).

With regard to claim 1, Forsman teaches amplifying a preselected nucleic acid sequence comprising the 16S/23S rRNA spacer region from several or all members of said predetermined group of pathogens (Abstract; p. 3492, col. 1, where the spacer region was amplified for sequencing; p. 3492, col. 1, where specific primers for each species were designed within the 16S/23S rRNA spacer region; p. 3494, Figure 1, Table 4).

Further regarding claim 1, neither Edwards nor Forsman explicitly teach the inclusion of an internal control template. Bergeron teaches the design of an internal control template for use in a LightCycler reaction (Abstract, p. 176).

With regard to claim 1, Bergeron teaches an embodiment comprising at least one internal control template, further comprising a hybridization reagent capable of specifically detecting said internal control template (p. 176, col. 1, ‘primers and probes’ heading, where genomic DNA and an internal control template were included in the amplification reaction and where pairs of hybridization probes for detection of the target and internal control were provided).

Regarding claim 1, neither Edwards, Forsman or Bergeron teach the specific plurality of hybridization probes of SEQ ID NO:3-5 and 8-9 targeted to the detection of enterococcus and

staphylococcus species. First, Bergeron '564 et al. (US Patent 6,001,564 December 1999) teaches the use of species specific primers and probes together with the use of "universal" primers and probes targeted to the 16S rRNA sequence for the combined detection of multiple bacterial pathogens.

With regard to claim 1, Bergeron '564 teaches a plurality of hybridization probes for the detection of enterococcus and staphylococcus species (Abstract, Annex I, Annex II, Table 1).

Regarding claim 1, Bergeron '564 does not teach the specific sequences of SEQ ID NO:3-5 and SEQ ID NO:8-9 as claimed. Kunsch '98 et al teaches a plurality of hybridization probes comprising a variety of sequences useful for the detection of Enterococcus faecalis.

With regard to claim 1, Kunsch '98 teaches a plurality of hybridization probes, wherein the hybridization reagents comprise SEQ ID NO:3 (see alignment below, where SEQ ID NO:973 of Kunsch comprises SEQ ID NO:3; p. 2, lines 33-35) and SEQ ID NO:5 (see alignment below, where SEQ ID NO:973 comprises SEQ ID NO:5; p. 2, lines 33-35).

SEQ ID NO:3

```
Qy          1 CTGGATATTGAAGTAAAAAGAATCAAAAC 29
              |||||||||||||||||||||||||||||
Db        355 CTGGATATTGAAGTAAAAAGAATCAAAAC 327
```

SEQ ID NO:5

```
Qy          1 ACCGAGAACACCGCGTTGAAT 21
              |||||||||||||||||||||
Db        324 ACCGAGAACACCGCGTTGAAT 304
```

Regarding claim 1, Kunsch '98 does not specifically teach SEQ ID NO:4 and 8-9.

With regard to claim 1, Naimi teaches a plurality of hybridization probes directed to the detection of Enterococcus faecalis, wherein the hybridization reagents comprise SEQ ID NO:4 (see alignment below, where SEQ ID NO:4977 of Kunsch comprises SEQ ID NO:8; p. 9, col. 1, where it is noted that the accession numbers for the nucleotide sequence data are provided, including X79343).

SEQ ID NO:4

```
Qy           4 ATTTGAAGTAAATGTAAGTAAT 25
               ||||||||||||||||||||||
Db           1 ATTTGAAGTAAATGTAAGTAAT 22
```

Regarding claim 1, neither Kunsch '98 or Naimi specifically teach SEQ ID NO:4 and 8-9. With regard to claim 1, Kunsch '97 teaches a plurality of hybridization probes, wherein the hybridization reagents comprise SEQ ID NO:8 (see alignment below, where SEQ ID NO:4977 of Kunsch comprises SEQ ID NO:8) and SEQ ID NO:9 (see alignment below, where SEQ ID NO:4750 comprises SEQ ID NO:9).

SEQ ID NO:8

```
Qy           1 CCGAGTGAATAAAGAGTTTTAAA 23
               |||||||||||||||||||||||
Db          35 CCGAGTGAATAAAGAGTTTTAAA 57
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SEQ ID NO:9

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Qy           1 GCTTGAATTCATAAGAAATAATCG 24
               ||||||||||||||||||||||||
Db          50 GCTTGAATTCATAAGAAATAATCG 73
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It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Edwards to target the 16S rRNA spacer

sequence as taught by Forsman to arrive at the claimed invention with a reasonable expectation for success. As taught by Forsman, “the 16S-23S rRNA intergenic spacer of the ribosomal RNA operon (rrN) has proven useful for identification of strains and species”. Forsman also notes “the high evolutionary rate makes it possible to distinguish closely related bacterial species” (p. 3492, col. 1). (Abstract). Finally, Forsman teaches “the variation between the 16S-23S spacer sequences of different mastitis pathogens made it possible to design specific primer pairs for each of the nine species considered in this study” and “primer pairs were selected so that the same PCR cycling conditions could be employed for all of them" (p. 3494, col. 2). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Edwards to target the 16S rRNA spacer sequence as taught by Forsman to achieve detection of a variety of species from within multiple genera using PCR amplification of the 16S-23S rRNA spacer region.

It also would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Edwards and Forsman to target the 16S rRNA sequences to a variety of bacterial targets, including enterococcus and staphylococcus as taught by Bergeron ‘564 and to arrive at the claimed invention with a reasonable expectation for success. As taught by Bergeron ‘564, “relates to DNA-based methods for universal bacterial detection, for specific detection of the common bacterial pathogens Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis, Streptococcus pneumoniae, Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Staphylococcus saprophyticus, Streptococcus pyogenes, Haemophilus influenzae and Moraxella catarrhalis as well as for specific detection of commonly encountered and clinically relevant bacterial

antibiotic resistance genes directly from clinical specimens or, alternatively, from a bacterial colony. The above bacterial species can account for as much as 80% of bacterial pathogens isolated in routine microbiology laboratories" (Abstract). Regarding universal detection, Bergeron '564 teaches "Testing clinical samples with universal probes or universal amplification primers to detect the presence of bacteria prior to specific identification and screen out the numerous negative specimens is thus useful as it saves costs and may rapidly orient the clinical management of the patients. Several oligonucleotides and amplification primers were therefore synthesized from highly conserved portions of bacterial 16S or 23S ribosomal RNA gene sequences available in data banks (Annexes III and IV). In hybridization tests, a pool of seven oligonucleotides (Annex I; Table 6) hybridized strongly to DNA from all bacterial species listed in Table 5" (col. 8, line 67 to col. 9, line 10). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Edwards and Forsman to target the 16S rRNA sequences to a variety of bacterial targets, including enterococcus and staphylococcus as taught by Bergeron '564 and to arrive at the claimed invention with a reasonable expectation for success.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the methods taught by Edwards and Forsman and Bergeron '564 to incorporate the internal control template as taught by Bergeron to arrive at the claimed invention with a reasonable expectation for success. As taught by Bergeron, "two pairs of fluorescently labeled adjacent hybridization probes, STB-F and STB-C and IC-F and IC-C, were also used for the rapid PCR assay to detect amplicons specific for group B streptococci and internal control amplicons, respectively" (p. 176, col. 1). Furthermore, Bergeron teaches,

"methods were specific and sensitive enough to detect a single genomic copy of group B streptococcus. The internal control was always amplified when S. agalactiae DNA was absent, thereby showing that negative PCR results for group B streptococci were not attributable to the presence of inhibitors in the clinical samples" (p. 176, col. 2). Additionally, Edwards and Bergeron share the same format for detection of the amplified samples, using analysis of hybridization of labeled probes and melt curve analysis. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the method taught by Edwards, Forsman and Bergeron '564 to incorporate the internal control template as taught by Bergeron to arrive at the claimed invention with a reasonable expectation for success.

Lowe teaches a method and computer program for designing primer pairs based on a set of rules regarding primer length, sequence composition, GC content, melting temperature, potential for primer dimer formation within a primer pair, and amplification product size, among other features. Lowe evaluated the performance of primers output by the computer program and after testing primers designed for more than 10 gene products found that "experimental testing has shown that all of the amplification products specified by these primers are of the predicted size and also hybridize with the appropriate cDNA or internal oligonucleotide probe" (p. 1760, col. 2). The computer program designed by Lowe can rapidly scan an entire nucleotide sequence "for all possible primer pairs obeying these rules" (p. 1757, col. 2). The process is based on a user specified region of the target sequence and other parameters including GC content and melting temperature of the amplified region. The program provides a list of candidate antisense primers based on scanning the sequence and locating GC-type sequences, "producing a 22-mer antisense primer 'candidate'" and selecting suitable primers by evaluating the GC content and

potential for self homology for each primer. The process is repeated for scanning and choosing candidate sense primers. After a bank of possible sense and antisense primers are produced from the input sequence “each suitable sense primer selected in this way is then checked for cross homologies" with all primers suitable for matching with it, based melting temperature of the amplification product and amplicon length. Finally, primer sets are approved and output in a format which includes the sense and antisense primer sequences, the melting temperatures and product length. The process is continued until the entire specified sequence has been scanned (p. 1758, col. 2). Considering the flexibility provided by this program and the ability to optimize individual primers and primer pairs, it would have been prima facie obvious to select and evaluate multiple candidate primer pairs for the amplification of a particular sequence.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Edwards, Forsman and Bergeron and the known sequences of Kunsch, Kunsch and Naimi to design a variety of primers and probes suitable for the amplification and detection of Enterococcus and Staphylococcus sequences, using the method of primer design taught by Lowe to arrive at the claimed invention with a reasonable expectation for success. Lowe teaches “a computer program which rapidly scans nucleic acid sequences to select all possible pairs of oligonucleotides suitable for use as primers to direct efficient DNA amplification” which allows for “the rapid selection of effective and specific primers from long gene sequences while providing a flexible choice of various primers to focus study on particular regions of interest". While the claims are drawn to a plurality of hybridization probes instead of specifically to primers, the issues of cross-hybridization, melting temperature and secondary structure important in the design of primer pairs is equally important

and relevant to the design of groups of oligonucleotides useful as hybridization probes. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Edwards, Forsman and Bergeron and the known sequences of Kunsch, Kunsch and Naimi to design a variety of primers and probes suitable for the amplification and detection of Enterococcus and Staphylococcus sequences, using the method of primer design taught by Lowe to achieve selection of a variety of specific primers and probes for efficient detection with a reasonable expectation for success.

Furthermore, regarding the design of primers and probes to a known sequence, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers and probes simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of bacterial species in clinical samples, and concerning which a biochemist of ordinary

skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers, a finding that would be applicable to oligonucleotides useful in other formats, including as hybridization probes. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18-mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

4. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards et al. (J. Clin. Micro., 2001, vol. 39, no. 9, p. 3047-3051, IDS reference) in view of Forsman et al.

(Microbiology, 1997, vol. 143, p. 3491-3500), Bergeron et al. (NEJM, 2000, vol. 343, no. 3, p. 175-179), Bergeron et al. (US Patent 6,001,564; December 1999, "Bergeron '564" herein), Kunsch et al. (WO98/50555; November 1998, "Kunsch '98" herein), Kunsch et al. (EP786519; July 1997, "Kunsch '97" herein), Naimi et al. (Sys. Appl. Micro. 1999, 22(1):9-21), Lowe et al. (Nucleic Acids Research, 1990, vol. 18, no. 7, p. 1757-1761) and Buck et al. (Biotechniques (1999) 27(3):528-536) as applied to claims 1-3 and 7 above, and further in view of Jannes et al. (WO96/00298; January 1996, IDS reference).

Edwards in view of Forsman, Bergeron, Kunsch 98, Kunsch 97, Naimi, Lowe and Buck teaches all of the limitations of claims 1-3 and 7 as recited in the 103 rejection stated above. However, neither Edwards, Forsman, Bergeron, Kunsch 98, Kunsch 97, Naimi, Lowe and Buck teaches detection of gram positive and negative bacteria.

With regard to claim 5, Jannes teaches an embodiment of claim 2, wherein gram positive pathogenic organisms are exclusively identified by said first amplification and detection reaction, and gram negative pathogenic organisms are exclusively identified by said second amplification and detection reaction (Example 3, p. 78, where Listeria, a gram positive organism is detected; Example 4, p. 84-86, where C. trachomatis, a gram negative organism is detected).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Edwards, Forsman and Bergeron to include the targets of gram positive and gram negative bacteria as taught by Jannes to arrive at the claimed invention with a reasonable expectation for success. As taught by Jannes, "the present invention relates to nucleic acid probes derived from the spacer region between 16S and 23S ribosomal ribonucleic acid (rRNA) genes, to be used for the specific detection of eubacterial

organisms in a biological sample by a hybridization procedure" (p. 1, lines 3-5). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Edwards, Forsman and Bergeron to include the targets of gram positive and gram negative bacteria as taught by Jannes to arrive at the claimed invention with a reasonable expectation for success.

5. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards et al. (J. Clin. Micro., 2001, vol. 39, no. 9, p. 3047-3051, IDS reference) in view of Forsman et al. (Microbiology, 1997, vol. 143, p. 3491-3500), Bergeron et al. (NEJM, 2000, vol. 343, no. 3, p. 175-179), Bergeron et al. (US Patent 6,001,564; December 1999, "Bergeron '564" herein), Kunsch et al. (WO98/50555; November 1998, "Kunsch '98" herein), Kunsch et al. (EP786519; July 1997, "Kunsch '97" herein), Naimi et al. (Sys. Appl. Micro. 1999, 22(1):9-21), Lowe et al. (Nucleic Acids Research, 1990, vol. 18, no. 7, p. 1757-1761) and Buck et al. (Biotechniques (1999) 27(3):528-536) as applied to claims 1-3 and 7 above and further in view of Loeffler et al. (Diagnostic Microbiology and Infectious Disease, 2000, vol. 38, p. 207-212).

Loeffler teaches a method of amplification and detection of pathogenic organisms through the detection of the 18S rRNA gene (Abstract).

With regard to claim 6, Loeffler teaches an embodiment of claim 3, wherein fungal pathogens are exclusively identified in said third amplification and detection reaction (Abstract, Table 1, where all of the pathogens identified are fungal pathogens).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the general teachings of Edwards, Forsman and Bergeron to

detect additional species, including yeast, as taught by Loeffler to arrive at the claimed invention with a reasonable expectation for success. While Edwards, Forsman and Bergeron are directed to the detection of bacterial species, one of ordinary skill would have recognized that the technique of species-specific detection using intergenic spacer regions as taught by Edwards and Forsman would be applicable to additional bacterial species and to yeast. Loeffler teaches the detection of yeast through targeting of the 18S rRNA spacer. As taught by Loeffler, “invasive candidiasis has become a major cause of morbidity and mortality in immune compromised hosts. Here we describe a fast and reliable DNA extraction and PCR amplification method in combination with slot blot hybridization assay” (Abstract). Loeffler also notes “the 18S rRA genes of 7 yeast species… were completely sequenced” and “primers described bind tightly to conserved primer binding sites" which “would allow rapid cycle sequence of additional ribosomal genes throughout the whole kingdom of fungi" (p. 207). Therefore, it would have been obvious to one of ordinary skill in the art to include additional steps for detection of other species present in clinical samples, such as yeast, as taught by Loeffler to arrive at the claimed invention with a predictable result.

Response to Arguments

Applicant's arguments filed April 10, 2010 have been fully considered but they are not persuasive. First, it is noted that the rejection above has been adjusted to address the specific concern raised in the instant remarks. However, the rejection has been maintained in view of the adjustment to the rejection.

Applicant traverses the rejection of claims 1-3 and 7 as being obvious over Edwards in view of Forsman, Bergeron, Bergeron, Kunsch, Kunsch, Naimi, Lowe and Buck. Applicant argues that “Figure 1 does not teach monitoring hybridization of each of said hybridization reagents at a pre-selected temperature" (p. 4 of remarks). Applicant summarizes the teaching in the specification regarding step bca and argues that “Edwards Figure 1 provides only a melting temperature profile and does not provide the required step of monitoring hybridization of each of said hybridization reagents at a single pre-selected temperature". Applicant argues that "Edwards provides a direct species only determination by melting curve analysis without any proceeding genus determination" and "only provides teachings on one genus - Staphylococcus" (p. 5 of remarks). Applicant then speculates that in a situation where samples could be present in a mixture that it is "possible that the different genera could result in similar melting temperature profiles" (p. 6 of remarks).

These arguments have been considered, but are not persuasive. While Applicant is correct that Figure 1 is not a true representation of the teaching of step bca) as argued by Applicant, it is noted that the materials and methods section of Edwards specifically teaches a step as taught and required by the specification regarding the practice of this step. For example, the specification teaches "steps bba) and bbb) are usually done together in such a way that first, the hybridization event itself is monitored at a pre-selected temperature. Then, the temperature is constitutively increased in order to determine the temperature at which the probe/target hybrid is being resolved. In other words, a melting curve analysis is performed” (p. 9 of remarks). Considering the newly cited passage in Edwards, on p. 3048, where fluorescence readings were taken after annealing at 55oC for 1 second, followed by the melt curve analysis. These readings

amount to a monitoring step prior to the melt analysis. Alternatively, in light of the teaching of the specification, the mere hold of the sample at 40 degrees prior to the start of the melt curve transition reads on this step, as well.

While Applicant argues that the step is useful for detection of genera, which is followed by species determination through the melt curve analysis, Applicant does not provide data supporting this step within the example or elsewhere in the specification. Therefore, it is not clear how this step, which can be practiced nearly simultaneously with the melt curve analysis, provides information regarding genera that is separate from the hybridization and melt curve analysis of step bcb. Therefore, Applicant's arguments are not persuasive and the rejection is maintained.

Applicant traverses the rejection of claims 5 and 6 further in view of additional references. Applicant argues that these rejections are not persuasive because neither Jannes nor Loeffler "teach or suggest the claim elements missing from Edwards as detailed above". These arguments are not persuasive for the same reasons as asserted above. The rejections are maintained.

Citation of Relevant Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Bialek et al. (Clinical and Diagnostic Laboratory Immunology, 2002, vol. 9, no. 2, p. 461-469) teaches detection of yeast in tissue samples by nested and real-time amplification (Abstract).

Conclusion

No claims are allowed. All claims stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Stephanie K. Mummert/

Primary Examiner, Art Unit 1637